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Review Article

# Coronavirus Disease-2019 (COVID-19): A Review of the Literature

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## Abstract

The ongoing outbreak of coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Fourteen mutations have been identified in Spike protein of SARS-CoV-2 of which mutation D614G is of urgent concern; that may have originated either in China or Europe, and which is now the dominant pandemic form in many countries. Although most patients have mild symptoms and good prognosis after infection but can result in severe and even fatal respiratory diseases such as acute respiratory distress syndrome (ARDS), can die of multiple organ failure. It still remains unclear regarding the pathogenesis of SARS-CoV-2 infection in humans. Innate immune response is the early defense against viral infections, and when it is dysregulated, results in an exaggerated inflammation, may cause death. The information on immune response to SARS-CoV-2 is not well documented. The cytokine storm may be responsible for severity of the disease. There is a growing understanding of SARS-CoV-2 in the virology, immunological changes, potential pathogenesis, disease progression and clinical management strategies. This review has summarized the current knowledge on the updated approaches regarding COVID-19 based on the emerging basic and clinical data.

**Keywords:** COVID-19; SARS-CoV-2; ACE2 Receptor; Cytokine Release Syndrome; IL-6; Hyaluronan; Time-LYM% Model (TLM); Lymphopenia; HLA Haplotype.

## Introduction

An acute respiratory tract infection, COVID-19, is a public health problem caused by 2019 novel Coronavirus (nCoV), first identified in Wuhan State of Hubei Province in China in December 2019, now is global concern of pandemic of unknown cause [1]. Chinese authorities reported several cases of pneumonia with an unidentified origin to World Health Organization (WHO) on December 31, 2019 [2]. On January 7, 2020, the 2019 novel Coronavirus (2019-nCoV; later renamed severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was confirmed as the cause of these reported cases, and the outbreak was subsequently named coronavirus disease -2019 (COVID-19) [3]. Its alarmingly quick transmission to many other countries across the world resulted in the World Health Organization (WHO) declaring a global health emergency on 30 January 2020 and COVID-19 pandemic [4].

Human coronavirus is one of the main pathogens of respiratory infection. There are seven coronaviruses of which SARS-CoV, MERS-CoV and SARS-CoV-2 responsible for severe disease; HKU1, NL63, OC43 and 229E are associated with mild symptoms [5]. The major SARS-CoV outbreak involving 8422 patients occurred during 2002-03 and spread to 29 countries globally [6]. MERS-CoV emerged in Middle Eastern countries in 2012 but was imported into China [7]. The sequence of SARS-CoV-2 is relatively different from the six other coronavirus subtypes but can be classified as betacoronavirus. SARS-CoV and MERS-CoV can be transmitted directly to humans from civets and dromedary camels, respectively, and both viruses originate in bats, but the origin of SARS-CoV-2 needs further investigation [8].

Korber B., *et al.* [9] have been identified fourteen mutations in Spike protein of SARS-CoV-2 of which mutation D614G is of urgent concern; that may have originated either in China or Europe, but begin to spread rapidly first in Europe in early February, and then in other parts of the world, and which is now the dominant pandemic form in many countries. Multiple strain infections in different countries may be due to recombination between locally circulating strains. Findings of this study have important implications

for SARS-CoV-2 transmission, pathogenesis and immune interventions [9].

SARS-CoV-2 transmission occurs in human with close contact. the Respiratory droplets produced after sneezing and enters in the mouth or nasal mucosa and lungs of people with inhaled air. Transmission rates are unknown for SARS-CoV-2; however, there is evidence of human-to-human transmission [10]. The mortality of SARS-CoV was more than 10% and MERS-CoV more than 35% [11]. A study by Chen., *et al*. showed the mortality by SARS-CoV-2 was 11% [12] resembling that in a previous study [13].

The clinical manifestations of COVID-19 are fever, cough, shortness of breath, muscle ache, headache, sore throat, confusion, rhinorrhea, chest pain, diarrhea, nausea and vomiting, bilateral pneumonia. SARS-CoV-2 infection is more likely to affect older males with comorbidities and can result in severe and even fatal respiratory diseases such as acute respiratory distress syndrome, can die of multiple organ failure [12].

At present, the potential pathogenesis, immune changes, clinical progression and potential treatment against SARS-CoV-2 are still unclear. This review has summarized the current knowledge on the updated approaches regarding COVID-19 based on the emerging basic and clinical data.

## SARS-CoV-2, receptor, cell entry

SARS-CoV-2 is an enveloped single positive-sense RNA virus, 50 - 200 nm in diameter [14]. Club-shaped glycoprotein spikes in the envelope give the virus a crown-like or coronal appearance.

SARS-CoV-2 have receptor-binding domain (RBD) in the spike protein that binds to ACE2 from humans, ferrets, cats and other species with high affinity because of receptor homology [14]. Angiotensin converting enzyme 2 (ACE2)-expressing cells are susceptible to 2019-nCoV infection, so ACE2 plays an important role in cellular entry [15].

At the S1-S2 boundary of the spike protein of SARS-CoV-2 has a functional polybasic (furin) cleavage site which is not present in SARS-CoV, which may be the cause of potential extension of tropism to the throat [16].

Potential infection routes of 2019-nCoV may depend on the expression and distribution of the ACE2 in human body. High expression of ACE2 receptor was found in type II alveolar cells (AT2) of lung [15,17], esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells, oral tissues, T cells, B cells and fibroblast [15,17]. Organs with high ACE2-expressing cells has been considered as potential high risk for 2019-nCoV infection [15]. SARS-CoV-1 and SARS-CoV-2, which share about 80% structural identity, enter host cells by utilizing ACE-2, expressed many cells in the body, including lung alveolar epithelial cells.

The envelope of SARS-CoV-2 studded with spikes--glycoproteins composed of two subunits. Subunit S1 binds to ACE-2 on the cell surface; subunit S2 fuses with the cell membrane. Another host enzyme, the serine protease, the type II transmembrane serine proteases (TMPRSS2), then promotes cellular entry of SARS-CoV-2 [18]. ACE-2 and TMPRSS2 are thus both essential for viral infectivity.

TMPRSS promotes entry of SARS-Cov-2 into cells by two separate mechanisms: ACE2 cleavage, which might promote viral uptake, and SARS-S cleavage, which activates the S protein for membrane fusion. According to proposed mechanism of SARS-CoV-2 cell entry (Figure 1) [19], after the S1 subunit (red) of the spike binds to the ACE-2 (blue) enzyme on the cell membrane surface, TMPRSS2 (brown) activates the spike and cleaves ACE-2. TMPRSS2 also acts on the S2 subunit (black) of the spike glycoprotein, causing an irreversible conformational change, activating it, and facilitating fusion of the virus to the cell membrane. The virus then enters the cell. A model of these events is shown in figure 1 [19].

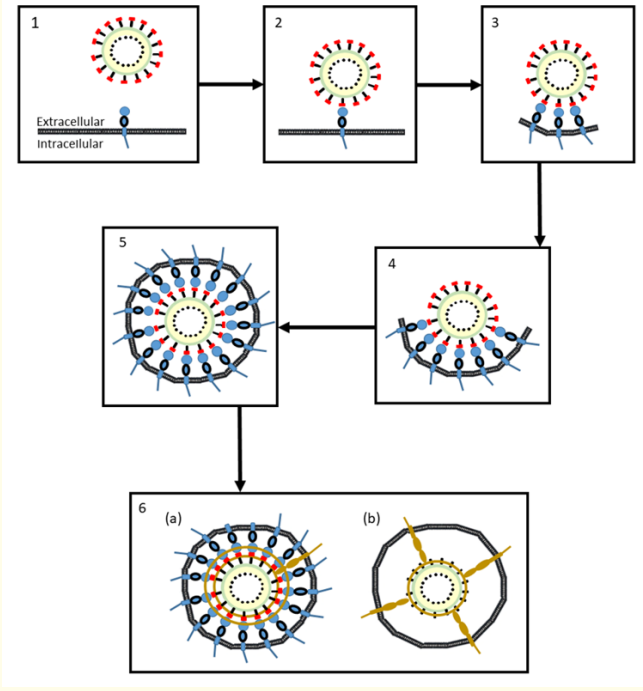


**Figure 1:** A proposed model of the mechanisms whereby coronavirus SRA-CoV-2 enters cells [19].

## Immune changes in SARS-CoV-2

Immune function is a strong defense against invasive pathogens. It has been revealed that the immune system played a vital role in defense against SARS-CoV and MERS infection. Immune changes in patients with SARS, MERS and influenza, especially changes in peripheral blood T lymphocyte subsets, contribute to understanding the characteristics, diagnosis, monitoring, prevention and treatment of the disease.

Disease severity of COVID-19 may be due to virus-induced direct cytopathic effects and viral evasion of host immune responses [20]. Innate immune response is the early defense against viral infections, and when it is dysregulated, results in an exaggerated inflammation, may cause death [21]. The information on immune response to SARS-CoV-2 is not well documented.

A study [22] reported dysregulated immune system in laboratory confirmed COVID-19 patients. The total number of B cells, both helper T cells (CD3+CD4+) and suppressor T cells (CD3+CD8+), regulatory T cells (both naïve and induced) and NK cells significantly decreased and more evident in the severe cases compared to the non-severe group. The function of CD4+, CD8+ T cells, and NK cells, was within normal range, significant difference was not found between two groups. The increase of neutrophil-to-lymphocyte ratio (NLR), were found in the severe group with COVID-19 compared to the mild group [22]. Another study confirmed the increase of NLR during the severe phase of COVID 19 [23], indicated that serious disturbance in internal environment and potential critical condition in those severe infected cases. NLR, a marker of systemic inflammation and infection, is considered as a predictor of bacterial infection, including pneumonia [24].

Low levels of CD4+T and CD8+T cells are common in severe 2019 novel coronavirus pneumonia (NCP). B cells and NK cells were also reduced both in mild and severe group but there was no significant difference. IL-6 and IL-10 levels were higher in severe patients but levels of IL-4, IL-10, IL-17, and TNF were within normal values. T cell subsets and cytokines can be used for differentiating mild form to severe. A study has to be done on large number of samples to confirm the "warning value" of CD4 + T, CD8 + T, IL-6 and IL-10 [25].

Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells control viral infection, and disease progression is correlated with the functional exhaustion of cytotoxic lymphocytes. Zheng M., *et al.* [26] showed that the total number of NK and CD8+ T cells was decreased markedly in COVID-19 patients and the function of NK and CD8+ T cells was exhausted with the increased expression of NKG2A. Expression of NKG2A was reduced with restored NK and CD8+ T cells level in patients convalescing after therapy. These findings suggest that SARS-CoV-2 infection is associated with the functional exhaustion of cytotoxic lymphocytes. It may be due to the fact that SARS-CoV-2 infection may break down antiviral immunity at an early stage [26]. NKG2A is an inhibitory receptor, it's expression on NK and CD8+ T cells induce functional exhaustion of NK and CD8+ T cells, leading to chronic viral infections [27]. For elimination of virus in the early stage of COVID-19 targeting NKG2A may prevent the functional exhaustion of cytotoxic lymphocytes [27].

Recent studies have illustrated that monocytes may be the main cause of exacerbation and even death of COVID-19 patients through inflammatory storms. The study by Zhou Y., *et al*. [28] showed that after the SARS-CoV-2 infection, CD4+ T lymphocytes are activated to T helper (Th) 1 cells and produces GM-CSF, IFN gamma, etc. The environmental cytokines induce inflammatory CD14+CD16+ monocytes which causes high expression of IL-6 and exaggerate the inflammation. These pathogenic Th1 cells and inflammatory monocytes may enter into the pulmonary circulation in large numbers and excessive non-effective host immune responses causes lung functional disability and quick mortality. Thus, monoclonal antibodies targeting GM-CSF or IL-6 may be effective in blocking inflammatory storms and, therefore, be a promising treatment of severe COVID-19 patients (Figure 2) [28]. Chuang Guo., *et al*. [29] identified a severe stage-specific monocyte subpopulation which creates a centre of immune cell interaction network connected by the inflammatory cytokines and their receptors. Although Tocilizumab (anti IL-6 receptor antibody) treatment attenuated overactivated immune response, yet immune cells including plasma B cells and CD8+ T cells continued to exhibit intense humoral and cell-mediated anti-virus immune response in recovered COVID-19 patients. These findings revealed the immunopathogenesis of severe COVID-19 as well as effectiveness of Tocilizumab treatment [29].

Tan L., *et al*. [30] suggested low LYM% as a predictor of prognosis in COVID-19 patients. In most cases LYM% was reduced to less than 5% within 2 weeks after disease onset. LYM% decreased initially in severe patients, increased to more than 10% until discharged. LYM% was more than 20% when discharged but fluctuated a little in moderate patients. These findings are in favor of suggesting lymphopenia as a predictor of prognosis in COVID-19 patients [30].

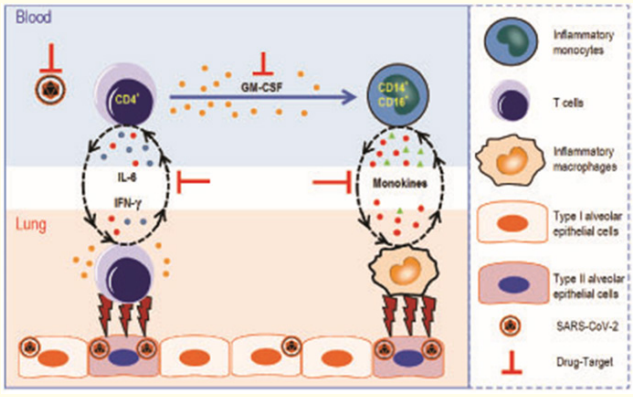


**Figure 2:** Pathogenic Th1 cells and inflammatory monocytes in severe COVID-19 [28].

Possible reasons for lymphopenia in COVID-19 patients may be due to the reasons that lymphocytes play a role in maintaining immune homeostasis. The potential mechanisms which may lead to lymphocyte deficiency: (1) As lymphocytes are expressing ACE2 receptor, may be a direct target of viruses causing lymphocyte death. (2) SARS-CoV-2 might directly damage the lymphatic organs such as thymus and spleen resulting in acute lymphocyte decline but which cannot be ruled out and needs to be confirmed by pathological dissection [30]. (3) Pro-inflammatory cytokines like tumor necrosis factor (TNF)α, interleukin (IL)-6, etc. leads to lymphocyte apoptosis and thereby induce lymphocyte deficiency. (4) Elevated blood lactic acid levels (hyperlactic acidemia) in severe COVID-19 patients, might suppress the proliferation of lymphocytes. Aforementioned mechanisms might cause lymphopenia in COVID-19 patients, which might damage lymphocytes, especially T lymphocytes, leading to impaired immune system [30].

Cytokines and chemokines are involved in SARS-CoV-2 infection from the initiation to the elongation phases of the disease [13]. Different cytokines are increased in initiation phase, including IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and vascular endothelial growth factor [13]. Cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNFα are increased in patients admitted to intensive care unit (ICU), compared to non-ICU patients [13].

In SARS-CoV and MERS-CoV patients the major cause of morbidity was Cytokine release syndrome (CRS). CRS is common in SARS-CoV-2 patients and acute respiratory distress syndrome (ARDS) is corelated with higher serum IL-6 level and adverse clinical outcomes [31]. Expression of C-reactive protein (CRP) is driven by IL-6, is also a biomarker of severe betacoronavirus infection.

Monocytes, macrophages, and dendritic cells infected by betacoronavirus are activated and secret IL-6 and other inflammatory cytokines. IL-6 has prominent proinflammatory properties which has been shown in figure 3 [32]. IL-6 can signal through two main pathways: classic cis signaling with Th 17 differentiation or trans signaling. Activation of these pathways can contribute to CRS resulting in severity of SARS-CoV-2 patients including hypotension and ARDS and IL-6 antagonist such as tocilizumab, sarilumab and siltuximab might ameliorate the disease (Figure 3) [32].

Clinical characteristics analysis of COVID-19 patients in a study showed that detectable serum SARS-CoV-2 viral load (RNAaemia) was diagnosed only in the critically ill group and seemed to reflect the severity of the disease. Furthermore, the level of inflammatory cytokine IL-6 in critically ill patients increased significantly, almost 10 times that in other patients. Notably, the extremely higher level of IL-6 was closely correlated with the detection of RNAaemia [33].

Increased IL-6 level in critically ill COVID-19 patients is still unknown. IL-6 as main contributor of cytokine storms increases the vascular permeability and impair the organ function, which might help to explain correlation of RNAaemia detection only in patients with an extremely high level of IL-6. The possibility that whether SARS-CoV-2 virus population explodes in a short period and triggers a cytokine storm with increased level of IL-6, could not be ruled out yet. Therefore, the combination of the IL-6 level and serum viral RNA Ct-value may be regarded as an effective marker for standard clinical measures to predict impending adverse outcomes with high accuracy [33].

## Potential pathogenesis, clinical progression, laboratory abnormalities

The pathogenesis of SARS-CoV-2 infection in humans remains unclear. Several studies have been done on COVID-19 and its pathogenesis [34], many people who are exposed to SARS-CoV-2 but not are infected and not all infected patients develop severe respiratory illness. A study in Wuhan analyzed over 1000 patients and revealed that it infects all age groups evenly, occasionally in children and adolescence. About 15% of COVID-19 patients progress to severe phase with a predominance of age over 65 years [34]. Good general health and an appropriate genetic background (e.g. HLA) is needed to boost up immune response at the incubation and non-severe stages that elicits specific antiviral immunity. The immune response to pathogens varies in individuals of different genetic background [35]. Polymorphisms in the MHC locus influence many critical biological traits and individuals' susceptibility to complex infectious diseases [36]. Different HLA haplotypes are associated

with distinct disease susceptibilities. Various infectious diseases are associated with specific HLA haplotypes such as tuberculosis, leprosy, HIV, hepatitis B, and influenza [37]. MHC class II haplotypes in murine are associated with the susceptibility to influenza. In human being, HLA class I is associated with H1N1 infections: HLA-A*11, HLA-B*35 and HLA-DRB1*10 are susceptible to influenza A(H1N1) pdm09 infection [38]. Accordingly, it seems advantageous to have HLA molecules with increased binding specificities to the SARS-CoV-2 virus peptides on the cell surface of antigen-presenting cells [35]. Specific HLA loci may be associated with the development of anti-SARS-CoV-2 immunity, so it is of utmost important to identify the alleles, either class I or II, that demonstrate induction of protective immunity [35].

The potential pathogenesis of SARS-CoV-2 infection in humans based on the published literatures of COVID-19 can be hypothesized. The virus enters the lungs by passing through the mucous membranes, especially nasal and larynx mucosa [34]. The virus may enter the peripheral blood from the lungs, causing viremia and attack organs which express ACE2, such as the lungs, heart, kidney, gastrointestinal tract. When the virus enters the blood from the lungs and then travels to the intestines, SARS-CoV-2 is more likely to be detected in the fecal samples [34].

The virus could lead to tissue damage by initiating innate immune response causing acute respiratory distress syndrome (ARDS), include short/rapid breathing, and cyanosis which is because of overwhelmed inflammation in the lungs resulting in respiratory failure and ultimate fatality [39]. Hyaluronan (HA) is associated with ARDS. HA has the ability to absorb water up to 1000 times its molecular weight which is revealed by CT images resembling white patches called “ground glass”, containing fluid in the lungs [23]. High levels of the cytokines (IL-1, TNF) are strong inducers of HA-synthase-2 (HAS2) in lung alveolar epithelial cells, and fibroblasts in COVID-19 patients [40]. Shi Y., *et al*. [35] stated in figure 4, that in non-severe stage, immune boosting by IFN alpha or antisera may be effective to elicit protective immune responses. Targeting IL-6 may be effective. Anti-IL-1 and anti-TNF therapy may also be effective. In severe stage, prescribing medical grade hyaluronidase and HAS2 inhibitor 4-MU would help in COVID-19 patients breathe by inhibition of hyaluronan synthase and elimination of hyaluronan which will clear the jelly of the lung. Cytokine (IFN gamma) activated mesenchymal stem cells can be used to block inflammation and promote tissue reparation. Vitamin B3 can be given to patients starting to have lung CT image abnormalities (Figure 4) [35].

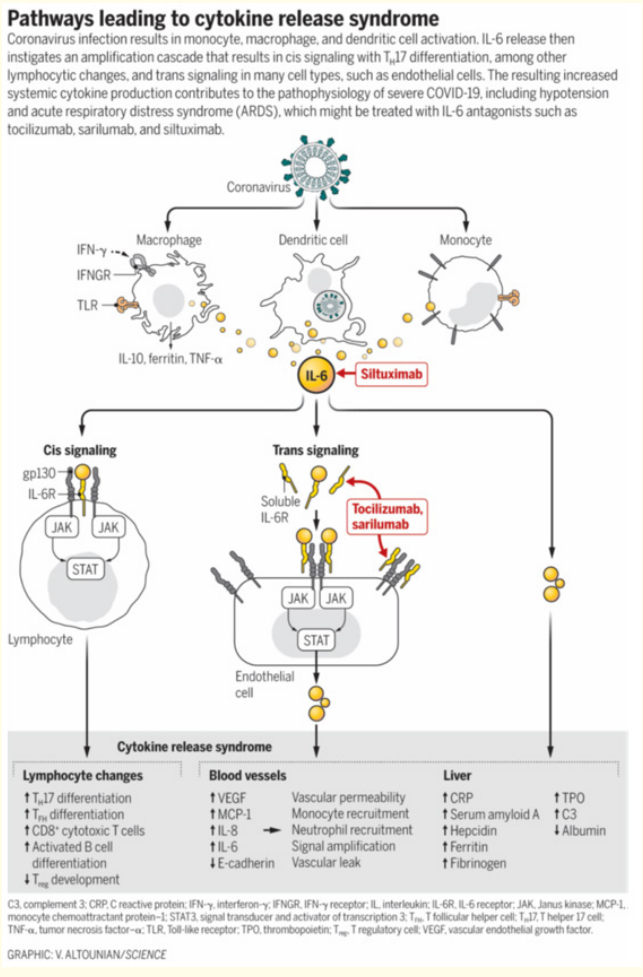


**Figure 3:** Pathways leading to cytokine release syndrome [32].

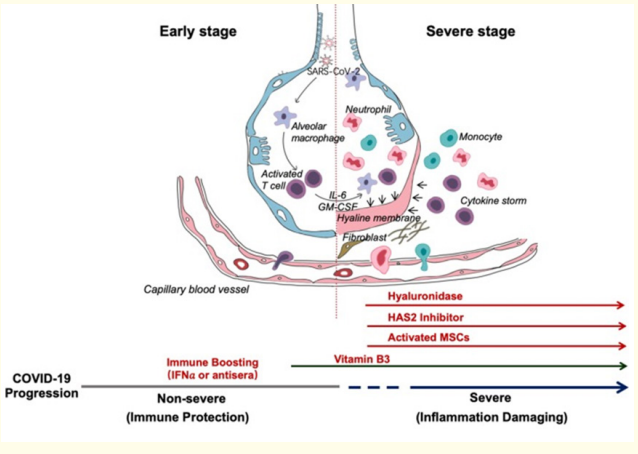


**Figure 4:** Schematic representation of the progression of COVID-19 infection and potential adjuvant interventions [35].

Lin L., *et al*. [41] stated in figure 5, that the clinical phase is divided into three: the viremia phase, the acute phase (pneumonia phase) and the recovery phase. If the immune function of patients in the acute phase (pneumonia phase) is effective, and no more basic diseases, the virus can be effectively suppressed, then enter the recovery phase (Figure 5) [41]. During the infection process, the white blood cell count in peripheral blood in the early stage of the disease is normal or slightly low [34] and there is lymphopenia, decreased B lymphocyte which may affect antibody production [23]. Lymphocytes were significantly reduced in severe type patients [23]. IL-6 were significantly increased, which also contributed to the aggravation of the disease around 7 - 14 days after onset. Non-survivors had higher levels of neutrophils, D-Dimer, blood urea nitrogen, and creatinine than the survivors [23]. Figure 5A and 5B is depicting the immune changes and therapeutic interventions in different phases of COVID -19 [41]. The immunocompromised patients with comorbidities, will become severe or critical type as the immune system cannot effectively control the virus in the acute phase (pneumonia phase). T cells, B cells were further reduced, while inflammatory cytokines and D-Dimer continued to increase in severe type patients (Figure 5A) [41]. The X-axis is the number of days after SARS-CoV-2 infection, and it is divided into three phases according to the above conjecture. The Y-axis is the trend of T cells, B cells, inflammatory factors, D-Dimer and viral load in patients (Figure 5A). The trend of each indicator in COVID-19 patients with severe type; (Figure 5B) The trend of each indicator in COVID-19 patients with severe type after LWMH and IVIg therapy. The shaded areas represent the recommended intervention times for LMWH and IVIg treatment [41].

A comparative study on the laboratory findings of Novel COVID-19 (NCOVID-19) pneumonia to other pneumonias (NON-NCOVID-19) on admission, except one NCOVID-19 patient, WBC count were in normal range whereas lymphocytes were decreased in NCOVID-19 and NON-NCOVID-19 patients. Both NCOVID-19 or NON-NCOVID-19 patients had Increased ratio of neutrophils. Compared to NON-NCOVID-19 patients, NCOVID-19 patients had higher levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GT) and α-hydroxybutyric dehydrogenase (α-HBDH). A proportion of NCOVID-19 patients had abnormally increased AST, ALT, γ-GT and LDH. Abnormally increased α-HBDH was seen in NCOVID-19 patients and NON-NCOVID-19 patients. Both NCOVID-19 and NON-NCOVID-19 patients had increased levels of CRP and IL6 but there was no significant difference between two groups. All patients had normal creatinine level [42].

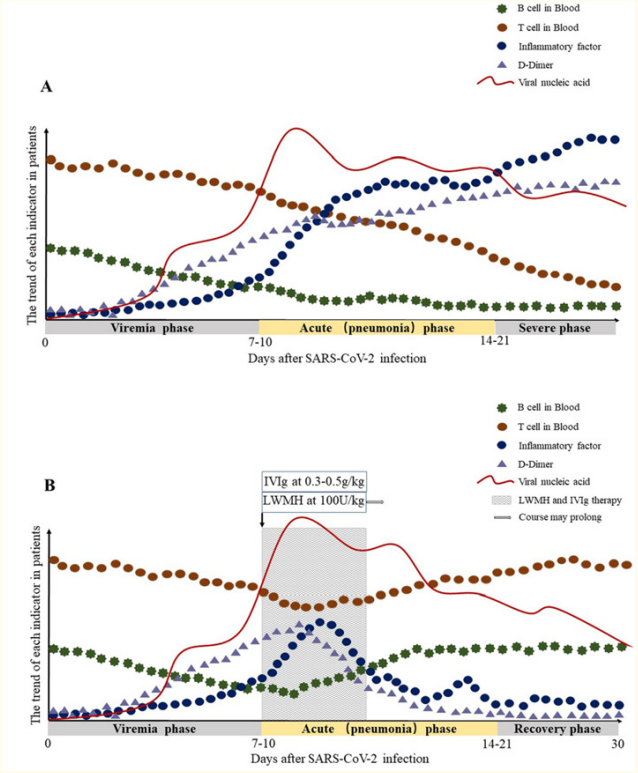


**Figure 5:** Hypothetical pathogenesis of COVID-19 [41].

On admission, 78.95% NCOVID-19 patients, had bilateral involvement, the typical feature is multiple lobular ground-glass opacity and subsegmental areas of consolidation in NCOVID-19 patients. Sequential CT images from same patient suggested that the inflammation was rapid infiltration in lobes of NCOVID-19 patients [42]. The 2019-nCoV infection caused similar onsets to other pneumonias. CT scan may be a reliable test for screening NCOVID-19 cases. Liver function damage is more frequent in NCOVID-19 than NON-NCOVID-19 patients. LDH and α-HBDH may be considerable markers for evaluation of NCOVID-19 [42].

Wang D., *et al*. [23] demonstrated that non-survivors had higher levels of neutrophils, D-Dimer, blood urea nitrogen, and creatinine than the survivors [23].

For disease classification and prognosis, Tan L., *et al.* [30] established a Time-LYM% model (TLM) as follows: patients have varying LYM% after the onset of COVID-19. At the 1st time point (TLM-1) of 10 - 12 days after symptom onset, patients with LYM% > 20% are classified as moderate type and can recover quickly. Patients with LYM% < 20% are initially classified as severe type. At the 2nd time

point (TLM-2) of 17 - 19 days after symptom onset, patients with LYM% > 20% are in recovery; patients with 5% < LYM% < 20% are still in danger and in need of supervision; patients with LYM% < 5% become critically ill with high mortality rate and need intensive care [30].

Serum SARS-CoV-2 viral RNA was detected in 15% of the COVID-19 patients [13], but the relevant characterizations are still lacking. In particular, it is unclear whether RNAaemia can be considered as a prognostic indicator, especially for severe or critically ill patients [33].

## Updated treatment approaches against SARS-CoV-2

### SARS-CoV-2 fusion/entry inhibition

A serine protease inhibitor, Camostat mesylate, a clinically proven inhibitor of TMPRSS2, significantly reduced lung cell line infection with SARS-CoV-2 and could be considered for COVID-19 treatment [18]. Arbidol and chloroquine phosphate is promising in COVID-19 treatment. Arbidol acts by inhibiting virus entry/fusion of viral membranes with cellular membranes. The molecular mechanism of chloroquine phosphate in the treatment of COVID-19 remains unclear, it could impair the endosome-mediated viral entry or the late stages of viral replication [43].

### SARS-CoV-2 replication disruption

Anti-viral agents against viral proteases, polymerases, MTases and entry proteins have been developed. A number of clinical trials of antiviral drugs are currently in progress, such as remdesivir (NCT04252664, NCT04257656), favipiravir (ChiCTR2000029600, ChiCTR2000029544), ASC09 (ChiCTR2000029603), lopinavir/ritonavir (ChiCTR2000029387, ChiCTR2000029468, ChiCTR2000029539), arbidol (ChiCTR2000029621). Remdesivir is the most promising antiviral for fighting SARS-CoV-2. Remdesivir is a monophosphoramidate prodrug of an adenosine analog. Its active form arrest RNA synthesis by incorporating into nascent viral RNA by RNA-dependent RNA polymerases (RdRps) [44].

### Suppression of excessive inflammatory response

Monoclonal antibodies targeting GM-CSF or IL-6 antagonist such as (tocilizumab, sarilumab and siltuximab) may be effective in blocking inflammatory storms and, therefore, be a promising treatment of severe COVID-19 patients [28,32]. Anti-IL-1 and anti-TNF therapy may also be effective. Clinical trials of anti-TNF therapy in COVID-19 patients suggest that the therapy should be initiated as early as possible [13]. Cytokine (IFN gamma) activated mesenchymal stem cells can be used to block inflammation and promote tissue reparation [35].

For elimination of virus in the early stage of COVID-19 targeting NKG2A may prevent the functional exhaustion of cytotoxic lymphocytes [27].

C3 signalling is positioned upstream in the innate immune cascade, so anti-inflammatory potential of AMY-101 which blocks C3 is promising [45], currently being tested in patients with COVID-19. By inhibiting C3, generation of C3a and C5a can be blocked simultaneously that can also block intrapulmonary C3 activation and IL-6 release from alveolar macrophages, or other cells that express C3a receptors (C3aRs) and/or C5a receptors (C5aRs), thereby ameliorating lung injury [45].

### Convalescent plasma therapy

With infections, when there is no specific therapy available, the therapy with convalescent plasma (CP) has been proposed as principal treatment [46]. Several clinical trials investigating the efficacy and safety of convalescent plasma transfusion in patients with COVID-19 are in progress (ChiCTR2000030010, ChiCTR2000030179, ChiCTR2000030381).

### Combined traditional Chinese and Western medicine treatment

Traditional Chinese Medicine (TCM)has been added in the latest treatment guideline in China as one of the treatment options for COVID-19. Wang et al. reported four cases with COVID-19 which gained improvement after taking combined Chinese and western medicine treatment [47]. The potential natural compounds that could target ACE2 for the potential treatment of COVID-19. By using molecular docking, Hansen Chen and Qiaohui Du [48] proposed that the five natural compounds, including baicalin, Scutellarin, Hesperetin, glycyrrhizin and Nicotianamine are potential compounds that target the ACE2 receptor and exert anti-virus effects for preventing 2019-nCoV infection [48].

### Vaccines

More than 15 potential vaccine candidates of COVID-19 are being developed around the world, including inactivated vaccine, recombinant subunits vaccine, nucleic acid-based vaccine, adenoviral vector vaccine, recombinant influenza viral vector vaccine, etc. The viral genome and its structural proteins have a direct tendency to impair immune surveillance. Protein sequences of SARS-CoV-2 has shown that there are eight HLA-DR epitopes located in the Spike, Envelope, and Membrane of the SARS-CoV-2 which might cause impairment of the immune surveillance [49]. Very recently Paul F., *et al*. [50] presented a self-amplifying RNA encoding the SARS-CoV-2 spike protein encapsulated within a lipid nanoparticle as a vaccine

and demonstrate induction of robust neutralization of a pseudovirus, proportional to quantity of specific IgG and of higher quantities than recovered COVID-19 patients. These data provide insight into the vaccine design and evaluation of immunogenicity to enable rapid translation to the clinic [50].

## Conclusion

2019-nCoV becomes a global health threat, still needs to be studied deeply. Further efforts should be given to know the whole spectrum and pathophysiology of the disease. Specific HLA loci may be associated with the development of anti-SARS-CoV-2 immunity, so it is of utmost important to identify the alleles, either class I or II, which can help to make plan for prevention, treatment, vaccination, and clinical approaches strategy. Multiple strain infections in different countries may be due to recombination between locally circulating strains, which may be the cause of dominant pandemic form in many countries. Due to the pandemic potentiality of SARS-CoV-2, careful surveillance is needed to monitor its future host adaption, transmission, pathogenesis and immune interventions.

## Ethical Approval

Not required.

## Declaration of Interests

The author declares no competing interests.

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